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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/332,522	06/14/99	COSTA M	7326-101

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PENNIE AND EDMONDS
1155 AVENUE OF THE AMERICAS
NEW YORK NY 10036-2711

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EXAMINER	
SHUKLA, R	
ART UNIT	**PAPER NUMBER**
1632	10

DATE MAILED: 10/06/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/332,522	Applicant(s) COSTA ET AL.	
	Examiner Ram R Shukla	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

1)☒ Responsive to communication(s) filed on *10 July 200* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-33* is/are pending in the application.

4a) Of the above claim(s) *5,19-21 and 29-33* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6-18 and 22-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of the CERTIFIED copies of the priority documents have been:

1.☐ received.

2.☐ received in Application No. (Series Code / Serial Number) _____ .

3.☐ received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *10* .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

DETAILED ACTION

1. Amendment filed 7-10-00 (paper # 9) has been entered.

2. Applicant's election without traverse of the invention of group I, claims 1-4, 6-18, and 22-28 in Paper No. 9 is acknowledged.

3. Claims 5, 19-21 and 29-33 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 9. As noted in the restriction requirements in the previous office action (paper # 6), claims 1-4, 6-18, and 22-28 will be examined to the extent they encompasses the elected subject matter.

Claim Rejections - 35 USC § 101

4. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

5. Claims 1 and 2 are rejected under 35 U.S.C. 101 because the claimed invention is directed to a non-statutory subject matter. In the instant case the invention recites a nematode which is genetically modified. Since there are spontaneous mutations or mutations due to chemicals present in nature, claimed invention would be a product of nature. Recitation of a transgenic nematode would be remedial.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-4 and 6-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic C. elegans whose genome comprises the endogenous ceSREBP gene and encodes the amino acid sequence of said ceSREBP disclosed in SEQ ID NO 2, wherein said endogenous ceSREBP has been mutated by transposon insertion mutagenesis, wherein said mutation results in a phenotype of early larval arrest, reduced pigmentation as a result of reduced number of lipid droplets in the intestine, and

arrest, reduced pigmentation as a result of reduced number of lipid droplets in the intestine, and accumulation of fluid filled vesicles, and uses of said transgenic C.elegans, does not reasonably provide enablement for any and all nematodes that have genetically modified expression or miss-expression of any and all SREBP proteins and uses of any and all such genetically modified nematodes. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would require undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue".

The specification as filed is not enabling for the claimed invention because the specification does not provide sufficient guidance as to how an artisan of skill would have made and used the claimed invention commensurate in scope with the claims without undue experimentation.

The specification teaches cloning of a C.elegans cDNA clone that encodes a protein (ceSREBP) that has sequence similarity in some regions of its amino acid sequence to SREBP proteins from human, mouse and Drosophila (see page page 41, lines 8-19). The specification also discloses different motifs of the putative protein. Additionally, the specification also teaches isolation of promoter sequences of the cloned cDNA and to use the promoter to express a marker gene in C.elegans which shows that the promoter directs the expression of genes in the intestine and pharynx during adult and developmental stages (see page 44, lines 19-27). The specification discloses that the inhibition of the function of ceSREBP by RNA interference method wherein antisense RNA was injected into the gonads or intestine (see page 46, lines 1-

6) and that the C.elegans so produced showed arrested larvae at L2 stage, pale intestine, reduction in the number and average size of pigmented lipid droplets in the intestine (see page 46, lines 20-36). The specification also teaches mutagenesis by transposon mutagenesis and that because of the larval arrest these mutants may not be propagated and therefore heterozygous strains were to be produced and that about 25% of the progeny of the mutants showed phenotypes of early larval arrest, reduced pigmentation as a result of reduced number of lipid droplets in the intestine, and accumulation of fluid filled vesicles (see page 55, lines 33-36 and page 56, lines 1-4).

First issue is, whether the specification is enabling for making and using any and all transgenic nematodes that express or mis-express any SREBP pathway protein or even every SREBP. The specification discloses the cloning of SREBP cDNA and mutation of the endogenous SREBP gene in C.elegans. However, the specification does not provide any disclosure as to what is the function of the ceSREBP. It is noted that the cloned SREBP disclosed in the instant application has sequence homology with SREBP of Drosophila or human SREBP2 or murine SREBP1 in different parts of the molecule. As disclosed in the specification, SREBPs are transcription factors that activate genes in cholesterol and fatty acid metabolism, and in vertebrates they can activate transcription of HMG-CoA synthase, HMG-CoA reductase, farnesyl diphosphate synthase, squalene synthase, fatty acid synthase, acetyl-CoA carboxylase, glycerol-3-phosphate acyltransferase, and acyl-CoA binding protein etc. (see page 1, lines 22-36). The specification does not teach which of these enzymes the SREBP of the claimed nucleic acid or protein regulates. Without this information, an artisan would not know which pathway, cholesterol synthesis or fatty synthesis pathway will the cloned protein play a role in. Even if one had to assume that ceSREBP functions in the lipid metabolism pathways, one would not know what all the unknown SREBPs encompassed by the claim would work and what would be result of mutation in the sequence of these genes. It would have taken undue experimentation to have made and practiced the claimed invention wherein any SREBP was mutated in C.elegans because there are more than one SREBPs known in humans or mouse (see last paragraph in column 2 on page 331 in Brown et al. Cell 89:331-340, 1997), and if one had to assume C.elegans had similar SREBP pathway, one would think it would also have multiple SREBPs which would regulate the function of different genes. Therefore, based on the specification filed one would not have known the result of such changes (phenotypes) in

all the SREPBs or whether observed phenotypes would have been same for all SREBPs or would have been same as observed in the instant case.

Next the issue is: whether the specification as filed is enabling for all the nematodes that would have SREBP or SREBPs mutated. Villee et al teach that the phylum nematoda has about 12,000 species of nematodes which occur in marine and fresh water and are parasites to domestic animals, plants, and humans (see Villee et al, chapter 24, pages 509-515, 1984). The specification does not teach whether all the nematodes would have same SREBP or different SREBPs or how related the SREBPs would be and whether the method of mutation taught would have produced the transgenic nematodes with same phenotype, particularly when nematodes can be less than a millimeter to 49 cms in length, which may affect the practicing of the method.

Next, the issue is: whether all the methods of creating genetic modification would have produced transgenic nematodes or C.elegans with same phenotype and whether the changes produced would have been inheritable. The example disclosed on page 46, lines 20-26 teaches that progeny of the microinjected animals showed several phenotypes, however, the specification does not teach for how many generations the genetic change was transmitted. If not, RNA interference method would be rather a transient expression method and may not produce transgenic nematodes. Regarding the method of chemical mutagenesis, it is noted that the specification has provided a review of methods of mutagenesis, however, no working examples have been disclosed. While the enablement of the method of chemical mutagenesis is not an issue, the issue is whether the mutant C.elegans would have same phenotype. In fact, the specification discloses that compared to the RNAi method, in the insertional mutagenesis method, about 25% of the heterozygous C.elegans showed the phenotype observed in RNAi method. Which indicates that all the methods may not produce same phenotypes, which may be either due to mutation in different parts of the gene, which may produce different effects on the activity of the protein itself resulting in variable phenotype. Therefore, based on the disclosure provided in the specification, an artisan of skill would not have known whether the C.elegans produced by three methods of mutagenesis would have same phenotypic effects and it would have taken undue experimentation to an artisan of skill to have made mutations by three methods and to figure out which phenotypes are really due to the SREBP protein.

The specification is not enabling for a nematode wherein SREBP protein is expressed using a heterologous protein because the specification has not provided any guidance as to what would have been the effect of the over expression of SREBP protein on the physiology of the animal and without this information an artisan of skill would not have known how to use such animals. Furthermore, it is noted that claims 8 and 9 recite animals that express or mis-express SREBP fragment or a part of the nucleic acid, again it is not clear how an artisan would have used such animals because the specification does not teach what would have been the phenotype of such animals or if the animals would have been viable at all. It is reiterated that the specification has not disclosed or taught what is the precise function of the SREBPs. Although one would know that the SREBPs protein might have a role to play in a pathway it does not indicate what is the precise role of the protein. Furthermore, the phenotype due to the mutation in the gene which may have resulted in the loss of the SREBP protein could not indicate that over expression would have the same effect on the animals. It is possible that block in the function of the protein may have affected another member of the pathway in addition to the function of the SREBP, whereas when it is overexpressed it may be affecting the activity of a different protein which may also be important for another pathway. Therefore, results obtained by inhibiting the function of a gene can not be correlated with the results obtained when same gene is being overexpressed. Regarding, the use of different promoters for expressing the protein, it is noted that one would not know that when the SREBP protein is expressed in gonadal cells, its effects would be the same as when it is expressed in the intestine or in any other organ. Again an artisan would not have known whether expression of the SREBP protein in different tissues or at different stages of development would have produced animals with same phenotype or what phenotype and without this information, an artisan would not have been able to distinguish all thee animals and would not have known how to use them.

Regarding claim 6 it is noted that the claimed invention is not enabled because while a marker gene can demonstrate the expression pattern of a gene in an animal, it can not provide any clue as to what would be the effect of the gene product on the physiology of the animal or what phenotypes would be produced if the gene product is over expressed in an animal. Regarding claim 11, it is noted that the specification does not teach or provide any evidence whether pale intestine or intestinal defects would have been observed when any SREBPs would

have been disrupted or its expression was inhibited. And as noted, the specification does not teach whether both over expression as well as inhibition of even ceSREBP will result in pale intestine. Furthermore, a truncated SREBP-2 in CHO cells, due to recombinations in the intron that terminates at codon 460, results in sterol resistant phenotype in these cells, however, no such event in SREBP has been observed (see last paragraph in column one on page 335). This would indicate that different SREBPs may undergo different processing and metabolism and therefore, phenotype due to their mutation or overexpression may vary. The specification as filed does not provide any guidance whether the same phenotype will be produced when the expression of any and all the SREBPs in C.elegans was altered. Regarding, claim 16 and 17 it is noted that as argued above, an artisan would not know what would be the phenotype of C.elegans that would have the expression of any and all SREBPs altered. Therefore, an artisan would not have known whether a fluorescently-labelled fatty acid conjugate would have been able to measure the lipid content in all the nematodes or C.elegans that would have altered expression of any and all SREBPs.

In conclusion, an artisan would not have been able to make and use the claimed invention commensurate in scope of the claims because the specification does not provide sufficient guidance and working examples for an artisan to practice the invention without undue experimentation and therefore, limiting the scope of the claimed invention to a transgenic C. elegans, wherein the endogenous ceSREBP gene of the said transgenic C.elegans wherein the nucleic acid sequence of ceSREBP is disclosed in SEQ ID NO 1 and the amino acid sequence of said ceSREBP is disclosed in SEQ ID NO 2, wherein said endogenous ceSREBP has been mutated by transposon insertion mutagenesis, wherein said mutation results in a phenotype of early larval arrest, reduced pigmentation as a result of reduced number of lipid droplets in the intestine, and accumulation of fluid filled vesicles, and uses of said transgenic C.elegans is proper.

8. Claims 1-4 and 6-11 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is referred to the revised interim guidelines on written description published December 21, 1999 in the Federal Register, Volume 64, Number 244, page 71427-71440(also available at www.uspto.gov).

In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. Since it is not realistic to expect that the "complete structure" of any transgenic animal, or even a cell, could be described, this requirement is interpreted to be whether phenotypic consequences of altering the genotype have been described. In this case, the specification provides example to make transgenic C.elegans (see pages 46-48). However, considering the fact that the claimed invention encompass all the transgenic nematodes which overexpress SREBPs or wherein the expression of SREBPs has been interrupted, the phenotypes and characteristics of all the nematodes may not be known and one would not know whether same phenotype would have been produced in all the nematodes. Additionally, an artisan would not have known what would have been the phenotype of all the nematodes or even C.elegans in which fragments of SREBPs or proteins of SREBPs encoded by fragments of SREBP encoding sequences were expressed.

Next, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics. It is not possible to adequately describe the claimed products because the effects of inactivating a gene can not be predicted, particularly when a gene product may be interacting with the proteins of a family of proteins. For example, Korach et al (US Patent No. 5,650550) produced a knockout mouse lacking a functional estrogen receptor. One skilled in the art would not have predicted that such an animal would even be viable (see col 9, lines 22-39), much less have been able to predict the resulting phenotype. In the instant application, it is not clear what would have been the result of the ablation of any and all SREBP genes, the normal function of which is not well established in all the nematodes or even in C.elegans in the transgenic nematodes encompassed by the invention. With the limited information disclosed in the specification, an artisan would have not been able to predict whether all the nematodes would have had same or different phenotypes compared to the transgenic C.elegans wherein ceSREBP expression was disrupted.

Therefore, the limited disclosure in the specification is not deemed sufficient to reasonably convey to one skilled in the art that Applicants were in possession of the huge genera recited in the claims at the time the application was filed. Thus it is concluded that the written description requirement is not satisfied for the claimed genera.

9. Claim 22, 26-28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a process of producing C.elegans SREBP wherein said C.elegans SREBP consists of the amino acid sequence disclosed in SEQ ID NO 2 by a culturing a host cell that comprises a vector wherein said vector comprises the nucleic acid sequence of SEQ ID NO 1, does not reasonably provide enablement any other embodiment. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification is not enabling for the host cells of claims 26 and 27 and the process of claim 28 because the specification as filed does not provide any guidance to make and use all the proteins that would have at least 8 contiguous amino acids of SEQ ID NO 2 commensurate in scope with claims 26-18 and an artisan of skill would not have known how to make all such proteins and use them without undue experimentation.

It is noted that claims 26-28 would encompass any protein that would have at least 8 contiguous amino acids of SEQ ID NO 2. However, the specification as filed does not provide any guidance whether all such proteins would have the activity of a SREBP protein. If not, the specification does not teach what other amino acids would have to be present in addition to 8 contiguous amino acids so that the protein will function as an SREBP. For example, the nucleic acids of HIV (disclosed in SEQ ID NO 28 of US Patent 5,919,462, filing date 5-17-96) would encode for a protein that would have at least 8 contiguous amino acids of SEQ ID NO 2 (see enclosed sequence results). However, it is not clear whether SEQ ID NO 28 of the cited US Patent would encode a SREBP or ceSREBP, if not, the specification does not provide any guidance as to how an artisan of skill would have used a host cell making such a protein or a yeast cell expressing such protein which was not ceSREBP. Similarly, World patent WO9102058 discloses a nucleic acid of 829 nucleotides and encodes a protein of 268 amino

acids and its the nucleic acid sequence form 456 to 482 would encode amino acids which would be same as 9 contiguous amino acids (227-235) of SEQ ID NO 2 (see sequence comparison results with SEQ ID NO 2). Again, the specification does not provide any guidance as to whether the protein encoded by the nucleic acid of WO9102058 would be a SREBP and to how an artisan of skill would have used a host cell making such a protein or a yeast cell expressing such protein which was not ceSREBP.

In conclusion, the specification as filed is not enabling for the process of producing any and all SREBP proteins that comprise at least 8 contiguous amino acids similar to residues 335-428 of SEQ ID NO 2 or that comprise at least 10 contiguous amino acids of SEQ ID NO 2 and therefore, limiting the invention of claims 22 and 26-28 to a process of producing C.elegans SREBP wherein said C.elegans SREBP consists of the amino acid sequence disclosed in SEQ ID NO 2 by a culturing a host cell that comprises a vector wherein said vector comprises the nucleic acid sequence of SEQ ID NO 1.

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 4, 5, 17 and 23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 17 is indefinite because it recites the trademark name BODIPY™. Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See Ex parte Simpson, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product and because a trademark is used to identify a source of goods, not the goods themselves. In the instant case, the trademark/trade name is used to identify/describe a fluorescently-labeled fatty acid conjugate and, accordingly, the identification/description is indefinite.

Claim 4 is indefinite because the term "said promoter" does not have an antecedent basis, since the base claim recites the term "a heterologous promoter."

Claim 23 is indefinite because it recites the term "appropriate." The term "appropriate" is a relative term and what may be appropriate in one instance may not be appropriate in another instance.

Claim Rejections - 35 USC § 102

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claims 22-26 are rejected under 35 U.S.C. 102(b) as being anticipated by Kohara et al (Seq Name gb_est47:D35004; Accession no D35004, published 08-08-1994).

Kohara et al disclose a C.elegans cDNA clone (YK15h12) which would encode a polypeptide comprising at least 10 contiguous amino acids of SEQ ID NO 2 or at least 8 contiguous amino acids of residues 335-428 of SEQ ID NO 2. The sequence disclosed by Kohara et al would encode a protein that would have 100% sequence identity with the amino acids 260-369 of SEQ ID NO 2. The nucleic acid sequence of D35004 has 99.7% sequence similarity in a region of 360 nucleotides with the nucleotide sequence of SEQ ID NO 1 and therefore, the sequence of Kohara et al would hybridize with the nucleic acid sequence of SEQ ID NO 1. A vector comprising the nucleic acid of Kohara et al and a host cell comprising such a vector is inherent to the teachings of Kohara et al because Kohara et al teach a particular clone and a library (see notes on the features) which is a vector and a collection of host cells.

Accordingly, the invention of claims 22-26 is anticipated by Kohara et al.

14. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ram R. Shukla whose telephone number is (703) 305-1677. The examiner can normally be reached on Monday through Friday from 7:30 am to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen Hauda, can be reached on (703) 305-6608. The fax phone number for this Group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 305-0196.

Ram R. Shukla, Ph.D.

Karen M. Hauda
KAREN M. HAUDA
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600